UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/529,010	11/22/2005	Chris Robert Lively	092633-0110	8892

22428 7590 06/16/2010

FOLEY AND LARDNER LLP
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

EXAMINER	
KELLY, ROBERT M	

ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
06/16/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/529,010	LIVELY ET AL.	
	Examiner	Art Unit	
	ROBERT M. KELLY	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 March 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,12,14-32,37-46 and 67-84* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7, 12, 14-32, 37-46, and 67-84* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment and argument of 3/22/10 is entered.

Claims 1, 14-16, 21, 25, 39, 46, 67, 74, and 78 are amended.

Claims 13, 38, 75, 80, 81, and 84 are cancelled.

Claims 85-87 are newly presented.

Claims 1-7, 12, 14-32, 37-46, and 67-84 are presently pending.

Election/Restrictions

Applicant has previously cancelled all claims drawn to non-elected inventions.

Claims 1-7, 12-32, 37-46, and 67-84 are presently considered.

Claim Status, Cancelled Claims

In light of the cancellation of Claims 13, 38, 75, 80, 81, and 84, all rejections and/or objections to such claims are withdrawn, as moot.

Non-Repeated Rejections

Any rejection not repeated is withdrawn.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant still has not complied with one

or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 60/414,097, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application.

The 60/414,097 Application fails to provide any of the data or information available in present Example 4 for support. Such support is the only support provided for the stability of these formulations. Hence, Applicant is denied priority to such document.

Response to Argument – Priority

Applicant argues that the priority document describes the particles claimed, and appreciates their surprising stability, citing pp. 3-4 they quote a generic statement of "thereby promoting shelf-life of the particles and the quality of the nucleic acid delivered to target cells intact.", to argue that they had possession of their "surprising or unexpected quality (p. 10, paragraph 1). Applicant points to various paragraphs where the polyArginines, the chelating agents, and the sugars are discussed, and argues that possession is had, although, they also describe only testing of the stability at temperatures of 4 and 60 deg C.

Such is not persuasive. There is no contemplation of 27 days at 40 deg C. Moreover, the following sentence in the same paragraph states that "Specifically, it has been found that nucleic acids can be ***stably attached to inert metal carrier particles in the presence of a nucleic acid condensing agent and a metal ion chelating agent***." It would appear that the stability from this paragraph is more about the fact that Applicant is arguing that they could not be stably attached. However, as is shown by the Art rejections, the Artisan did know this already. Moreover, the next paragraph argues for use of neutral pH, rather than alkaline pH to preserve nucleic acid integrity, and also washing of the condensed nucleic acid, and protection from nucleases. Overall, taken in context, this appears to argue that stability has to do with other than storage at 40 deg C temperature. Moreover, the claim does not even require the particles to be so-stored, and so, if this Applicant's contribution to the science, their contribution is not even required to be taken advantage of in the claims. Such would argue that the claims are not commensurate with Applicant's "invention". With regard to the possession arguments and listing, in alternative embodiments, different options for the condensing agent, the chelators, and the sugars, while the Examiner will agree that the polyArg alone is meant to apply to all combinations, the further specific chelator, and the remaining general on the sugars fails to provide for more than an obviousness-type support. Moreover, simply put, Applicant did not even evince an intent to test the substances at 40 deg C, and to do so for 27 days, at the filing of the priority documents, and hence, there is simply to contemplation to evince possession under the statute. At best, the possession argued is one of obviousness.

Claim Rejections - 35 USC § 112 – Clarity

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

In light of the amendments, the rejections of Claims 1-7, 12-32, 37-46, and 67-83 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, are withdrawn.

To wit, the issues have been cleared up.

Claim Rejections - 35 USC § 112 – New Matter

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7, 12, 14-32, 37, 39-46, 67-74, 76-79, and 82-84 remain rejected and Claims 85-87 are newly rejected, under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for comprising new matter, for reasons of record, as modified by the amendments. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for reasons of record, as modified by the new claimed scope.

Applicant's claims are drawn to a generic inert metal carrier, onto which a generic polyArg, from 2-3 amino acids in length and a generic nucleic acid are precipitated, in the presence of EDTA and a generic sugar, and the particles are dried, and have a half-life of at least

27 days at 40 deg C. The dependent claims are all generic in each of these aspects, to various degrees.

New claim 85 attempts to grab at the single working embodiment of DTPA, by grabbing at the sucrose, and then applying it to all embodiments of chelator, and specifically DTPA in the dependent claim, Claim 86.

Example 1 determines specific experiments that demonstrate that specific sugars and salts have differing influences on DNA yield, physical stability of DNA or particles (pp. 25-29), that precipitations using various ratios of protamine sulfate, EDTA, water, and either trehalose, sucrose, or lactose provide for stability (pp. 29-31), although the actual data of stability is withheld, so the Examiner simply take the word of Applicant that the stability is similar.

As is shown in the prosecution history, Applicant's sole support for the generic embodiments claimed is found in TABLE 2. However, table 2 is limited in several ways: (i) it is limited to gold particles, (ii) it is limited to tetraarginine peptides, and (iii) it is limited to a single nucleic acid. Moreover, the amounts of sugar of 30% in all embodiments shown here, and the amount of chelator is 5mM in all embodiments found here, and there is an exclusion of ethanol in the compositions (TABLE 3). There is an analysis of two embodiments of the scope of sugars, covering sucrose and trehalose, in combination with two chelators: EDTA and DTPA.

However, it should be specifically noted that this is the first demonstrated intent to claim a group of particles of the scope of these particles, by way excluding the non-working embodiment of the table (DTPA and trehalose; TA101.4), and moving the working embodiment that is within the scope of the generic stability (DTPA and sucrose; TA101.3) into a new claim. However, the Artisan would never considered as possessed these excluded these embodiments

from the generic claims, as clearly, the paragraph after TABLE 2 states "This indicates that the chelator EDTA was more stabilizing than DTPA, but there was little difference between trehalose (3 and 4) and sucrose (1 and 2) as formulated into these powders." (p. 33, paragraph bridging the Tables). Moreover, this simple statement also indicates "these powders", which indicates an intent to limit the results into the powders which were formed, not a generic powder as presently claimed. Lastly, (i) these specific embodiments, of a single metal, a single nucleic acid, and a single polyarginine, fail to provide support for the generic metal, the generic nucleic acid, and the generic polyarginine claimed, as a single embodiment never provides support for a genera; and (ii) the quoted statement above demonstrates that the results are limited to "these powders".

Hence, given that there is no specific indication in the Art to extrapolate to other embodiments, Applicant having been the first to flesh-out and "optimize both stability of nucleic acid attached to carrier particles, thereby promoting shelf-life of the particles and the quantity of nucleic acid delivered to target cells intact, and also expression ...", there is simply not demonstration of possession of the subgenera meant to be fleshed-out by the specific embodiments demonstrated.

Simply put, it is clear that Applicant's amendment again provide even further evidence that they wish to further analyse the data they have provided, and carve around all non-working embodiments while losing as little as possible to obtain the maximum coverage, while overcoming rejections of record, but such post-filing analysis is necessarily one of obviousness, as it requires analysis of the embodiment demonstrated to arrive at generas which are not specifically disclosed. This is just the sort of thing that new matter rejections are meant to

exclude from happening. In essence, the finding of possession requires an analysis of the prosecution history, and extrapolation to new genrae given the rejections at hand, rather than a clear evincing of possession.

Therefore, the Artisan would not have understood Applicant to have been in possession of the invention as claimed at the time of filing.

Response to Argument – new matter

Applicant's argument of 3/22/10 has been fully considered but is not found persuasive.

Applicant argues that when the disclosure clearly discloses the claimed invention, there is no new matter issue (p. 14, paragraph 1).

Such is not persuasive. Applicant's specification contains no explicit recitation of the generic embodiments claimed, and the specific embodiments demonstrated do not demonstrate possession of the embodiments which are not shown, as it would require an obviousness-type analysis to reach such conclusion, which does not amount to a demonstration of possession.

Applicant argues that they have amended to remove the 25% of embodiments demonstrated which do not fall within the desired stability measurement of the claims (p. 14, last two paragraphs).

Such is not persuasive. While the shown embodiment which does not work is now removed from the claims, the claims are still extremely large. By way of example, the non-working embodiment (DTPA and trehalose) argues that either DTPA, trehalose, or their combination provides for non-working embodiments, but there is simply no way to determine whether under a generic sugar, EDTA was possessed for working at least 27 days at 40 deg C, or that under a generic chelator, trehalose was possessed. What the Examiner is trying to

communicate is that there are many stability studies performed, that stability is discussed in the specification in terms of *in vivo*, shelf-life which is not limited to dried particles, or 40 deg C, or 27 days, stability at other temperatures, and various other aspects. To determine that Applicant possessed a generic chelator with trehalose, or a generic sugar with EDTA is simply a post-prosecution guess. Moreover, given that only one sugar is shown to work with DTPA and one chelator is shown to work with trehalose, these are essentially single embodiment combinations, which fails to provide support for a generic embodiment, in addition to the single metal, single nucleic acid, and single polyarginine peptide.

Applicant points to the declaration of Dr. White, to argue that they have met the Examiner's suggestion that a declaration would help to demonstrate to the Examiner that Applicant possessed the claimed generic embodiment (p. 15, paragraph 1).

Such is not persuasive. The Examiner first most strongly suggested case law on the point of whether a New Matter rejection was proper when only a few digital embodiments of a generic claim are provided by the original filing, which Applicant did not provide. Second, with regard to the declaration, it was clearly stated that the Expert must provide evidence and analyze it to determine that "one of skill in the Art" (I believe the word "Artisan" was utilized, but the meaning was conveyed), would have understood that Applicant had conveyed the genera claimed as an invention. However, Paragraphs 9-12 only conclude that "to scientists skilled in the technology (acceptable terminology for one of skill in the Art) ... disclosed in Table 2 ... expressly described DNA coated-particles produced using formulations containing an arginine, a metal chelating agent, and a sugar. Table 2 also expressly described that such particles, ... had a half-life of [] at least 27 days"; "a knowledgeable person, informed by the data in Table 2, woudl

have understood that the inventors of the '010 application realized that they had prepared relevant particles ..."; and that "wherein the particles suitable for delivery have a half life of at least 27 days at 40 [deg C]' is clearly described in the specification of the present application and, therefore, the inventors "had possession" of the invention at the time of filing." These conclusions clearly provide for a possession of embodiments encompassed, which are relevant particles, and Dr. White utilizes this to conclude "possession". However, Dr. White, being an expert in science, clearly does not understand possession as a legal concept. Possessed embodiments within a scope are clearly not a demonstration of a possessed genera when such genera is one made by way of amendment, as such is an obviousness-type analysis, and Dr. White's analysis is clearly one of obviousness, as there is no evincing of possession, but a finding that it is obvious to claim these embodiments, as they fit the numbers demonstrated, and to exclude those that do not fit the numbers. However, there is no Art cited to logically, in any way, demonstrate that such a jump of logic could be made. Hence, unfortunately, Dr. White has not provided an analysis which demonstrates possession in terms of the law, but only obviousness, which may be possession in his own opinion, but does not fit with patent law.

Applicant quotes paragraph 11 of Dr. White to argue that the statement "a knowledgeable person, informed by the data presented in Table 2, would have understood that the inventors of the '010 application realized that they had prepared relevant particles having a half-life of at least 27 days at 40 [deg C]." (p. 15, penultimate paragraph).

Such is not persuasive. Of course they realized they had prepared particles within all generas which the particles fall within, however, did they specifically contemplate the genera

they are claiming? No, there is no evidence of this. To get to the specific genera, it has to be more than an obviousness-type support.

Lastly, it should be noted that Claim 67, and dependent claims, have gone unanswered in the rejection in that is no support for the absence of sugars and the half-life argued, even in the form of specific embodiments encompassed.

Note for Art rejections: The Examiner considered the amendment to dried particles, but does not consider the "unexpected result" to be more than optimization of conditions, as specifically shown in the specification (p. 3, penultimate paragraph). As such, there is no unexpected result which would preclude obviousness-type rejections. The Artisan was already of the understanding that the sugars would stabilize the compositions, and the elucidation of how much is simply such an optimization.

Claim Rejections - 35 USC § 103 – Sanford/Balhorn (Oard)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5, 7, 12, 17-20, 22-30, 32, 37, 42-45, 67, and 73 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,204,253 to Sanford, et al., and Balhorn, et al. (2000) Molecular Reproduction and Development, 56: 230-34, as evidenced by

Oard (1993) Plant Cell, Tissue and Organ Culture, 33(3): 247-50, and further in view of U.S. Patent No. 6,641,553 to Chee, et al., for reasons of record and as necessitated by amendment.

The reasoning is repeated for clarity of record, and the new claims are addressed:

With regard to Claims 1-3, 7, 17-18, 25, 27, 28, 32, and 42-43 Sanford teaches M-10 series tungsten microprojectile particles (which range from 0.3 to 2.1 micrometers in diameter (e.g., Oard (1993) Plant Cell, Tissue and Organ Culture, 33(3): 247-50, p. 249, col. 1, paragraph 3), coated with DNA condensed in the presence of spermidine, and also in the presence of EDTA (e.g., col. 15, paragraph 2) and also in the presence of calcium chloride (e.g., Id.), and the methods of making claimed (e.g., Id.).

With regard to Claims 4-5, 28-29, Sanford teaches that a transgene for, *inter alia*, kanamycin resistance, is transformed into the cells, and further expressed (EXAMPLE 2). Kanamycin is a fungal protein, and hence, a Fungal antigen.

With regard to Claims 19-20, 44-45, the particles are subsequently contacted with ethanol (e.g., col. 15, paragraph 3).

With regard to Claims 22-24, Sanford teaches a needless syringe device, as it has no needle, but injects the particles into cells (e.g., Figure 1), and which contains a receptacle containing the particles for delivery (e.g., FIGURES 5a-5b).

With regard to Claim 26, Sanford teaches the addition of the spermidine to the mixture containing the microparticles and DNA (e.g., col. 15, paragraph 2).

However, with regard to all rejected claims, Sanford fails to teach the use of arginine of the formula $[Arg]_{2\text{-}10}$ or a physiologically acceptable salt thereof .

However, the purpose of spermidine in condensing the DNA is to provide compact particles, resistant to degradation, as taught in the Art by Balhorn, et al. (2000) Molecular Reproduction and Development, 56: 230-34, e.g., p. 230, paragraph bridging columns. Further, Balhorn teaches that transformations of somatic cells and sperm are improved by the faster release of the DNA from condensation by the use of small polymers of polyArginine, and specifically, for the highest change in off-rate, those between 6-12 arginines having the greatest release kinetics (e.g., p. 233, paragraph bridging columns). Still further, Balhorn teaches that by simply changing the amount of arginines in the polyArginine in such delivery methods, the length of time required to dissociate from the polyArginine could be tailored for each individual delivery system (e.g., p. 233, column 2, paragraph 2), and hence, tetraarginine (Claim 73) would be found upon routine experimentation.

Further, with regard to the presence of EDTA on the surface of the particle (e.g., Claim 67), absent reason to believe otherwise, these particles do have EDTA on their surface.

Lastly, Chee teaches that microprojectile particles are dried for use (e.g., Detailed Description, paragraph 22).

Hence, at the time of invention, it would have been obvious to modify the microprojectile particles of Sanford with the use of the polyarginines of Balhorn, to arrive at the claimed invention of Dried particles as taught by Chee. The Artisan would have been motivated to do so to arrive at the desired release kinetics for any specific system and apply it through

microprojectile. Moreover, the Artisan would have had a reasonable expectation of success, as Balhorn had already demonstrated the release kinetics to be improved.

Response to Argument – Sanford/Balhorn evidenced by Oard, and now also Chee

Applicant's argument of 3/22/10 has been fully considered but is not found persuasive.

Applicant argues that Sanford is limited to spermidine teaching, and CaCl condensation, that Oard is limited to CaCl2, and the only teaching is that prior to precipitation, the DNA is rinsed with poly-L-Lysine (p. 16).

Such is not persuasive. With regard to being "limited to their teachings only" such is wrong. The rejection is one of obviousness, not anticipation. Moreover, it is taken in the context of the skill and knowledge of the Artisan at the time of invention. The rejection clearly demonstrates the skill that the Artisan would be able to apply to the Art at the time of invention. Moreover, with regard to poly-L-Lysine, reduction in clumping clearly means that it works. Still further, the rejection is to poly-L-arginine, as taught in Balhorn. Still further, Oard teaches that the solution was subject to clumping, however, the dried composition is not subject to such clumping as it is dried, it simply not in a freely-mixing phase. Lastly, Applicant has not even shown that their composition clumps do not clump. The argument is a red herring. Gold flakes reduce clumping, poly-L-lysine reduces clumping, and the short polyArginine peptides increase release kinetics.

Applicant makes of record their understanding that the reason for utilizing polyArginine is for the use (the release kinetics) of the DNA condensates (p. 17, paragraph 2).

Such is clearly the rejection of record, as above.

Applicant has amended the claims to recite "drying" the particles, thereby overcoming the rejection (p. 17, paragraph 3).

Such is not persuasive. The rejection is now altered due to the amendment to include Chee, to demonstrate that the Artisan understood that the particles could be dried.

Applicant begins to make the argument that the Examiner's reasoning is distinct from Applicant's reasoning, for making the particles (p. 17, last paragraph).

Such is accepted but makes no difference, as the result is not unexpected, but simply an optimization by claiming those particles that are most stable.

Applicant argues that the Artisna would not be motivated to make a dried powder if the polyarginine is utilized for solution release kinetics (p. 18, first paragraph).

Such is not persuasive. The artisan would dry the particles as it is an art-recognized condition for application of particles by way of gene gun.

Applicant broadly avers that the particles would be less stable, stating that the stability of the particles is considered less if the particles cause increased dissociation (p. 18, paragraph 2).

Such is not persuasive. As has been explained and reexplained in the record and the interview previously had, the precipitate is not subject to release kinetics in solution. It is not in solution. The Examiner has provided the proper equilibrium equations and shown how mass-action removes the possibility of increased release kinetics while dried. Is there something that Applicant does not understand about the basic chemistry involved?

Applicant argues that because the solution property is what Balhorn is about, teaches away from its use in a dried particle (p. 18, penultimate paragraph).

Such is not persuasive. The Artisan understands that the dried particles are solvated upon application. If they were not, the gene would never get into the cell and be active within the cell. This would thwart the purpose of utilizing dried particles at all under any circumstances. However, Applicant does appear to recognize in their specification that dried particles are normally understood in the Art, and further, Chee also recognizes it.

Applicant relies on Adami to argue again that the dried particles would never utilize polyArginine, becuase the dissociation is associated with the solution particles (pp. 18-19, paragraph bridging).

Such is not persuasive. The dried particles become solvated upon application, otherwise, it would be non-useful-for-transforming-of-a-cell DNA sitting there, like dirt. The Examiner has explained this, and yet, Applicant appears to refuse to understand the mechanisms through which a gene gun particle is solvated from the precipitate into a new environment when it is in the tissue. Still further, to the point, the Artisan clearly understood that the precipiated DNA on the particle dissolves from the microparticle and can be expressed by a cell once applied *in vivo* (e.g., U.S. Patent No. 6,303,330 to Croteau, 10 paragraphs before the Examples). Clearly, the Artisan understands this, and the Examiner is truly puzzled as to why Applicant does not, when they are an expert.

Applicant argues that the stability is surprising and unexpected, and nothing in the Art cited demonstrates the temperatures or time frames of stability for the dried particles (pp. 19-20, paragraph bridging).

Such is not persuasive. Even Applicant has described their disclosure as "optimization" (e.g., p. 3 of the SPECIFICATION), and as shown in the Art rejection below, stability was

expected. How much, and in particular, at the unusual temperature chosen by Applicant, is simply an optimization of what is known.

Claim Rejections - 35 USC § 103, Sanford, Balhorn (Oard), Cherng, Kwok

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5, 7, 12, 14, 15, 17-30, 32-36, 37, 39, 40, 42-46, 67, 73, 79, 82, and 83 remain rejected, and Claims 85-87 are newly rejected, under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,204,253 to Sanford, et al., and Balhorn, et al. (2000) Molecular Reproduction and Development, 56: 230-34, as evidenced by Oard (1993) Plant Cell, Tissue and Organ Culture, 33(3): 247-50 and U.S. Patent No. 6,641,553 to Chee, et al., as applied to claims 1-5, 7, 12, 17-20, 22-30, 32-37, 42-45, 67, 73, above, and further in view of Oard (1993) Plant Cell, Tissue, and Organ Culture, 33(3): 247-50 and Cherng, et al. (1999) Pharmaceutical Research, 16(9): 1417-23 and Kwok, et al. (2000) International Journal of Pharmaceutics, 203: 81-88, and U.S. Patent No. 5,780,295 to Livesey, et al., as necessitated by amendment and to further strengthen the rejection.

With regard to the claims rejected above, as is shown above, Sanford and Balhorn and Chee, as further evidenced by Oard, make obvious the various aspects of the claims.

However, Sanford and Balhorn, as further evidenced by Oard, do not make obvious the use of gold particles, further condensed in the presence of sucrose.

On the other hand, Oard teaches the use of gold particles can reduce particle clumping (e.g., p. 249, paragraph bridging columns). Further, Cherng teaches that condensation of nucleic acids with cationic polymers is further stabilized for storage by the presence of sucrose during the condensation (e.g., ABSTRACT).

With regard to Claims 79, 82, and 83, as shown in the above rejection, from Balhorn, it is routine experimentation to arrive at tetraarginine peptides, as well as heptaarginine peptides.

With regard to Claim 80, as shown above, it was known to conduct the precipitations on the microparticle in the presence of EDTA.

Kwok teaches that, e.g., sucrose can be used in as an excipient to stablize DNA condensates (e.g., p. 82).

Still further, Livesey demonstrates that it was well known that sucrose, and several other sugars were known to provide for cryoprotection and dry protection (e.g., Detailed Description, paragraphs 30 and 31)

Hence, at the time of invention, it would have been obvious to modify the techniques of Sanford and Balhorn, as further evidenced by Oard, to use the gold particles of Oard to reduce clumping, and further to condense the DNA in the presence of sucrose as taught by Cherng/Kwok, to increase the stability of the condensed DNA over time. Moreover, the Artisan would have had a reasonable expectation of success, as Oard teaches that gold particles will reduce clumping and Cherng/Kwok taught that the sucrose present in the condensed solution would provide more stability.

Response to Argument – Sanford, Balhorn (Oard), Cherng/Kwok

Applicant's argument of 3/22/10 has been fully considered but is not found persuasive.

Applicant broadly avers that Cherng does not overcome the deficiencies of the base rejection (p. 20, paragraph 3).

Such is not persuasive. There is no such deficiency.

Applicant argues that Cherng is not teaching precipitates onto metal particles, and therefore, is irrelevant to stability when the metal particles are added to the system, and there is no mention of inert metal particles, citing p. 1423 of Cherng, second paragraph (p. 20, penultimate paragraph).

Such is not persuasive. First, the citation takes Cherng out of its intended meaning. To wit, Cherng states, in the last paragraph:

> In conclusion, we have demonstrated that PDMAEMA-pCMV lac Z plasmid complexes are stable when stored in aqueous solution at low temperature. The stability of this system could even be increased by lyophilization. A lyophilized [sp?] formulation preserved almost its full transfection potential when aged just below the glass transition temperature of the sucrose matrix. Although these findings are stricly [sp?] speaking only applicable for PDMAEMA-pCMV lacZ plasmid formulations, the results might be extended to other polyplex and lipoplex formulations.

The Examiner understands this to mean that the exact numbers provided are strictly applicable to the complexes used, and other formulations, e.g., with PEI, might provide for distinct numbers, however, the overall trends are deemed to be known. Still further, to believe that Cherng's results are only for those particles studied fails to provide what the Artisan would think after reading Kwok and Livesey, which appear to take for granted that it is known that these compounds stabilize the complexes of the polycation/DNA. The Artisan is not limited to the literal words and taking such out of context to be read in a vacuum, but instead understands the Art. The Art clearly demonstrates and understanding that sugars stabilize these complexes.

Lastly, if the particles are "inert", as Applicant argues (and the Examiner agrees), they do not significantly change anything about the precipitated system, as they are inert.

Again, Applicant provides the opposite argument, that Cherng is excluded from applicability in view of the Art, but is to be read strictly (pp. 20-21, paragraph bridging).

Such is not persuasive. Whatever the board may think is fine, but the Examiner stays with the argument that the statement is meant to be read to mean the exact data may not be exactly the same, but the broad trends are going to be similar. Still further, such limitation is in conflict with the further understanding of Kwok and Livesey. How would anyone limit these findings, when the Art is wrought with several writings of the ability to stabilize the complexes in question.

Applicant argues that Kwok is irrelevant, as it "relates to freeze-dried DNA/poly-lysine condensates", not precipitation of DNA onto metal particles and provides no insight on the properties of stability at 40 deg C or room temperature (p. 21, paragraph 2).

Such is not persuasive. Freeze-dried DNA/poly-lysine condensates ARE precipitates. Applicant's claims are not a DNA precipitate in the absence of condensates. The metal particle is simply the surface onto which it precipitates, not a major affector in the system. The properties of stability are irrelevant, as the stability is already established by Kwok, by Cherng, and by Livesey. Again, Applicant appears to be completely confused as to what the difference is between precipitation and condensation, as well as the effects of the "inert" metal particle.

Applicant argues that Cherng and Kwok fail to overcome the shortcomings of the base references (p. 21, paragraph 3).

Such is not persuasive. There is no such shortcoming.

Claim Rejections - 35 USC § 103, Sanford, Balhorn (Oard),Chee, Livesey, Cherng, Barman(Livesey)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-7, 12, 14-32, 37, 39-46, 67-73, 76, 79, 82, 83 and 85-87 remain and/or are newly rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,204,253 to Sanford, et al., and Balhorn, et al. (2000) Molecular Reproduction and Development, 56: 230-34, as evidenced by Oard (1993) Plant Cell, Tissue and Organ Culture, 33(3): 247-50, and further in view of Oard (1993) Plant Cell, Tissue, and Organ Culture, 33(3): 247-50 and Cherng, et al. (1999) Pharmaceutical Research, 16(9): 1417-23, and Kwok, et al. (2000) International Journal of Pharmaceutics, 203: 81-88, U.S. Patent No. 6,641,553 to Chee, et al., and U.S. Patent No. 5,780,295 to Livesey, et al., as applied to claims 1-5, 7, 12, 14, 15, 17-30, 32-36, 37, 39, 40, 42-46, 67, 73, 79, 82, 83, and 85-87 above, and further in view of U.S. Patent Publication No. 2004/0142475 to Barman, et al, as further evidenced by U.S. Patent No. 6,194,136 to Livesey, et al., for reasons of record and to emphasize the arguments.

As shown above, Claims 1-5, 7, 12, 14, 15, 17-30, 32-36, 37, 39, 40, 42-46, 67, 73, 79, 82, 83, and 85-87 are obvious over the Art cited, except the cited Art does not specifically teach the use of transgenes encoding therapeutic proteins, or the use of a combination of raffinose and

sucrose to stabilize the DNA. Nor does the cited art teach or make obvious the transgenes encoding HPV, HIV, HSV2, HSV1 or Hepatitis B antigens.

On the other hand, Barman teaches that stabilizers such as saccharides may be used in combination to stabilize the nucleic acid protein complexes (e.g., paragraph 0054). Further, Barman teaches that HPV, HIV, HBV, and HSV (which includes HSV1 and HSV 2), antigens can be the transgenes for expression of antigens (paragraph 0036). Still further, Barman teaches influenza virus antigens to induce antibody responses (e.g., paragraph 0117). Still further Livesey also demonstrates the general understanding in the Art that various stabilizers which are sugars include raffinose (DESCRIPTION OF THE PREFERRED EMBODIMENTS, paragraph 29).

Hence, at the time of invention, it would have been obvious to modify the cited Art with Barman to use both raffinose and sucrose in stabilizing the particles and/or to use the various cited virus proteins. The Artisan would have been motivated to do so as the art already recognized that the sugars could be used in combination and/or the various proteins could be expressed for making antigens. Moreover, the Artisan would have had a reasonable expectation of success, as the Art already recognized the efficacious effect of saccharides.

Response to Argument – Sanford, Balhorn (Oard), Cherng/Kwok, Chee, Livesey, and Barman(Livesey)

Applicant's argument of 8/7/09 has been fully considered but is not found persuasive.

Applicant reiterates the deficiencies of the base references (pp. 21-22, paragraph bridging).

Such is not persuasive. There are no such deficiencies.

Applicant argues that Barman and Livesey fail to provide the various other portions of the claims other than what they specifically say (p. 22, paragraph 2).

Such is not persuasive. This is a rejection for obviousness, not anticipation.

Applicant broadly avers hindsight reconstruction (p. 22, paragraph 3).

Such is not persuasive. The number of references required is not evidence of hindsight reconstruction, unless it cites Applicant's reference. Necessarily there is an amount of hindsight reconstruction in the form of what is required to be demosntrated. However, such is not what is legally considered hindsight reconstruction. The references demonstrate an understanding of the system, and further demonstrate that the various portions may be utilized for their Art-recognized purposes. Such is obviousness, not hindsight reconstruction, as the legal concept is of hindsight reconstruction is understood.

Claim Rejections - 35 USC § 103 – many references

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-7, 12, 14-32, 37, 39-46, 67-74, 76-79, 82, 83 and 85-87 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,204,253 to Sanford, et al., and Balhorn, et al. (2000) Molecular Reproduction and Development, 56: 230-34, as evidenced by Oard (1993) Plant Cell, Tissue and Organ Culture, 33(3): 247-50, and further in view of Oard (1993) Plant Cell, Tissue, and Organ Culture, 33(3): 247-50 and Cherng, et al. (1999)

Pharmaceutical Research, 16(9): 1417-23, and Kwok, et al. (2000) International Journal of Pharmaceutics, 203: 81-88; U.S. Patent No. 6,641,553 to Chee, et al., and U.S. Patent No. 5,780,295 to Livesey, et al., and U.S. Patent Publication No. 2004/0142475 to Barman, et al, as further evidenced by U.S. Patent No. 6,194,136 to Livesey, et al., as applied to claims 1-7, 12, 14-32, 37, 39-46, 67-73, 76, 79, 82, 83 and 85-87 above, and further in view of the knowledge of the Artisan as evidenced by (i) Ramos, et al. (1997) Applied and Environmental Microbiology (e.g., ABSTRACT); (ii) Ericksson, et al. (2003) Pharmaceutical Research, 20(9): 1437-43 (e.g., ABSTRACT); (iii) Kaushik, et al. (2003) Journal of Biological Chemistry, 278(29): 26485-65 (e.g., ABSTRACT); (iv) Garg, et al. (2002) Proceedings of the National Academy of Science, USA., 99(25): 15898-903 (e.g., ABSTRACT); (v) More, et al. (1998) Hindustan Antibiotics Bulletin, 40(1-4): 1-4 (ABSTRACT ONLY); (vi) Joshi, et al. (2001) AAPS PharmSciTech., 2(4): 25 (ABSTRACT ONLY), Ruan, et al. (2003) European Journal of Biochemistry, 270: 1654-61 (e.g., ABSTRACT), and Schellman (2003) Biophysical Journal, 85(1): 108-25.

As shown above, the various references obviate the various claims, however, Claims 74, 75, 77, and 78 introduce the requirement of trehalose as the sugar, and the combination of gold particles precipitated with DNA in the presence of polyarginine, EDTA, and trehalose. Hence, the new aspect is essentially the use of trehalose.

However, as shown by the abstracts of (i) Ramos, et al. (1997) Applied and Environmental Microbiology, 63(10): 4020-25 (e.g., ABSTRACT); (ii) Ericksson, et al. (2003) Pharmaceutical Research, 20(9): 1437-43 (e.g., ABSTRACT); (iii) Kaushik, et al. (2003) Journal of Biological Chemistry, 278(29): 26485-65 (e.g., ABSTRACT); (iv) Garg, et al. (2002) Proceedings of the National Academy of Science, USA., 99(25): 15898-903 (e.g., ABSTRACT);

(v) More, et al. (1998) Hindustan Antibiotics Bulletin, 40(1-4): 1-4 (ABSTRACT ONLY); (vi) Joshi, et al. (2001) AAPS PharmSciTech., 2(4): 25 (ABSTRACT ONLY), and (vi) Ruan, et al. (2003) European Journal of Biochemistry, 270: 1654-61, many sugars, and especially Trehalose is known to stabilize proteins, especially when the product is being dried. Still further, this stabilizing force is even generally understood to be due to the changes in excluded volume and contact interaction with the surface protein, which is increased in the presence of sugars in general, and shown in Schellman (2003) Biophysical Journal, 85(1): 108-25, (e.g., ABSTRACT). Given this, it is clear that the Artisan would have understood that the molecules would be stabilized in the presence of various sugars, and particularly trehalose and sucrose.

Hence, it would be obvious to perform the various steps with trehalose, or really any particular sugar. The Artisan would do because it would allow increased stability to be imparted to the dried particles, and thereby allow their half-life to be increased. Moreover, the Artisan would have a reasonable expectation of success, as the Artisan knew that trehalose was efficient at stabilizing such.

Response to Argument – Sanford, Balhorn (Oard), Cherng/Kwok, Barman(Livesey) and Various Other References

Applicant's argument of 3/22/10 has been fully considered but is not found persuasive.

Applicant argues that the additional references fail to overcome the deficiencies of the base reference(s) (p. 23, paragraph 2).

Such is not persuasive. The references have no such deficiencies.

Applicant argues that the lengthy references are not directed to any technology similar to Applicant's claimed particles, much less the "surprising" characteristics of the present invention,

and the use of many references do not make up for the base references deficiencies (p. 23, paragraph 3).

Such is not persuasive. The references demonstrate what is generally known as a water-is-wet reference. It shows that it is understood that proteins and DNA and protein-DNA complexes are stabilized by sugars in general, and that trehalose and sucrose are known as stabilizers. Still further, Schellman demonstrates an understanding of why it occurs. Hence, the references together demonstrates what is a water-is-wet concept: sugars, and particularly trehalose, stabilize proteins and DNA and complexes thereof, by way of exluded volume and contact interaction. Such does not change because it was precipitated on an inert product (in this case an inert metal). There is no reasoning to provide for such an analysis. If there was, the Examiner would be happy to drop the rejection(s).

Conclusion

No Claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ROBERT M. KELLY whose telephone number is (571)272-0729. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Robert M Kelly/
Primary Examiner, Art Unit 1633